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EXAMINER	
LYLES, JOHNALYN D	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,842	MASLIAH ET AL.	
	Examiner	Art Unit	
	Johnalyn Lyles	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-39* is/are pending in the application.

4a) Of the above claim(s) *29-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *16-39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

The Examiner of U.S. Patent application SN 09/806,842 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Lyles, Technology Center 1600, Art Unit 1647.

The amendment filed on 11-23-04 has been entered into the record and has been fully considered. Claims 1-15 have been cancelled. Claims 16-39 are pending. Claims 29-39 have been withdrawn, and claims 16-28 are presented for examination.

Election/Restrictions

Applicant's election without traverse of Group I, claims 16-28, in the reply filed on 11-23-04 is acknowledged.

Claims 29-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11-23-04.

Claim Rejections - 35 USC § 112, First paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Applicants new claims recite: a method for identifying an inhibitor of NACP/α-synuclein aggregation comprising providing a test compound, inducing NACP/α-synuclein aggregation by subjecting the samples to a metal-ion catalyzed oxidative condition, and measuring the aggregation level of NACP/α-synuclein in the samples, wherein less aggregation is indicative that the test compound is an inhibitor of NACP/α-synuclein aggregation. Applicant has not provided support for the claim amendments as recited and the Examiner fails to find apparent support. Thus, the recited method constitutes new matter absent evidence of support in the specification as originally filed.

The new matter is noted to extend to Applicant's 371 priority document of PCT /US99/23134, 10-6-1999 and the provisional 60/103,310, 10-6-1998 as filed. As set forth below, priority therefore cannot be established. As the instant specification is a mirror of the 371 filing, Applicant's response should address how support for the claimed methods may be found within instant application as well as the provisional application of 60/103,310 if Applicant's are to obtain the benefit of the earliest priority date. Applicants should particularly address amendments to the claims as submitted 8-5-04 including all new limitations.

Applicants argue as set forth in p. 7 of the 8-5-04 response.

Applicant's arguments at p. 7 of the 8-5-04 response have been fully considered but are not persuasive. In particular, Applicants point to support for the new claims within the specification and provisional application at pp. 22-24, Examples 1 and 2 and p. 28, Example 8 of the specification. While such support that ferric ion and ferrous ion with hydrogen peroxide are capable of inducing aggregation, it is noted that such does not apparently address the scope of claims 16-23 as directed to "a metal-ion catalyzed oxidative condition" or to claims 24-26 as directed to "wherein the metal-ion catalyzed oxidative condition comprise iron ions" or "the iron ions comprise a ferrous ion" or "the iron ions comprise a ferrous chloride". While iron catalyzed oxidation is noted to be effective in the provisional, the provisional and specification further note that other metals were ineffective in promoting aggregation, see in particular p. 24, lines 11-14 and Hashimoto *et. al.*, in which cupric and manganese ions and hydrogen peroxide alone were incapable of promoting NACP/α-synuclein aggregation. Furthermore, Hashimoto *et. al.* suggests ferric ion produced by the Fenton reaction (ferrous ion with hydrogen peroxide) is responsible for the aggregation of NACP/α-synuclein.

As to the recitation in claims 24-26, there is no apparent evidence (other than with ferric ion and ferrous ion with hydrogen peroxide) that ferrous ion alone or in combination with anything other than hydrogen peroxide or metal-ion catalyzed oxidative conditions that comprise iron ions would be effective to promote aggregation of NACP/α-synuclein. The recitation in claims 24-26 of "comprise iron ions" and "iron ions comprise" reads on metal-ion catalyzed oxidative conditions with iron and agents other than hydrogen peroxide. Thus, while iron-catalyzed oxidative conditions wherein the iron ion is ferric ion or ferrous ion with hydrogen peroxide are apparently supported in claim 25-26, the broad recitation of a metal-ion catalyzed

oxidative condition and "iron ions" other than ferric ion and ferrous ion with hydrogen peroxide appears to be new matter absent further support for these broader recitations.

Claims 16-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description requirement**. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of identifying an inhibitor of NACP/α-synuclein aggregation comprising providing a test compound, a first sample and a second sample, wherein each sample comprises NACP/α-synuclein; inducing NACP/α-synuclein aggregation in the first sample and second sample by subjecting them to a metal-ion catalyzed oxidative condition; exposing the first sample to the test compound; measuring an aggregation level of NACP/α-synuclein in the first sample and the second sample; and comparing the aggregation level of NACP/α-synuclein in the first sample and with the aggregation level of the second sample, wherein less aggregation in the first sample is indicative that the test compound is an inhibitor of NACP/α-synuclein aggregation.

The claims, as written, encompass a wide variety of metal-ion catalyzed oxidative conditions. The instant disclosure of an iron-catalyzed oxidative condition does not adequately describe the scope of the use of the claimed genus metal-ions including but not limited to iron, aluminum and copper (pg 5, line 7).

A description of a genus of metal-ion catalyzed oxidative conditions may be achieved by means of a recitation of a representative number of species, defined by a specific structure and/or

function, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. A genus claim may be supported by a representative number of species as set forth in Regents of the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

The instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of metal-ion catalyzed oxidative conditions. There is no description of the metal-ions, which are critical to the structure and function of the genus of metal-ion catalyzed oxidative conditions as claimed. Structural features that could distinguish the metal ions in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the metal-ion catalyzed oxidative conditions encompassed. No identifying characteristic of the metal-ion catalyzed oxidative conditions is provided such that one of skill would be able to predictably identify the encompassed metal-ion catalyzed oxidative conditions as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly varying, the disclosure of iron-catalyzed oxidative conditions is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to

describe, enable and use the genus as broadly claimed. One skilled artisan cannot envision the structure of the encompassed metal-ion catalyzed oxidative conditions as claimed, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of producing a metal-ion catalyzed oxidative condition. Adequate written description requires more than a mere statement that it is part of the invention and reference to potential conditions. Vas-cath, Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-cath, page 1116).

Claims 17-18 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description requirement**. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of identifying an inhibitor of NACP/α-synuclein aggregation wherein the aggregation inhibitor comprises: a non-amyloidogenic protein that inhibits aggregation of NACP/α-synuclein or an agent that promotes the expression of anti-amyloidogenic proteins. The claims, as written, encompass a wide variety of non-amyloidogenic proteins and agents that promote the expression of anti-amyloidogenic proteins. The instant disclosure of b-synuclein as an inhibitor of α-synuclein aggregation (see example 8) does not adequately describe the scope of the use of the claimed genus of non-amyloidogenic proteins or

agents that promote the expression of anti-amyloidogenic proteins. A description of a genus of non-amyloidogenic proteins or agents that promote the expression of anti-amyloidogenic proteins may be achieved by means of a recitation of a representative number of species, defined by a specific structure and/or function, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. The instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of non-amyloidogenic proteins or agents that promote the expression of anti-amyloidogenic proteins. There are no structural features that could distinguish the non-amyloidogenic proteins or the agents that promote the expression of anti-amyloidogenic proteins in the genus from others excluded are missing from the disclosure or such that one of skill would be able to predictably identify the encompassed non-amyloidogenic proteins or agents that promote the expression of anti-amyloidogenic proteins as being identical to those instantly claimed. Since the disclosure fails to provide a representative number of species to describe, enable, and use the genus as broadly claimed and the skilled artisan cannot envision the structure of the encompassed non-amyloidogenic proteins or agents that promote the expression of anti-amyloidogenic proteins as claimed, adequate written description is not achieved. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-cath, page 1116).

Claims 16-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing aggregation of α-synuclein via exposure to ferric ion or ferrous ion with hydrogen peroxide, does not reasonably provide **enablement** for inducing such

aggregation via exposure to any metal-ion catalyzed oxidative condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims.

Applicant's specification teaches the exposure to ferric ion alone and ferrous ion with hydrogen peroxide is sufficient to provide for α-synuclein aggregate formation. The specification further teaches that cupric and manganese ions and hydrogen peroxide alone were incapable of promoting NACP/α-synuclein aggregation. The art and specification are silent as to what other metal-ion catalyzed oxidative conditions are capable of inducing α-synuclein; the specification notes also β-amyloid has been shown to exhibit oxidative damage in neurons and to stimulate aggregate formation of α-synuclein. Thus, there is no apparent evidence other than with ferrous ion and hydrogen peroxide that metal-ion catalyzed oxidative conditions would be effective to promote aggregation of NACP/α-synuclein. Thus, while ferric iron and ferrous iron with hydrogen peroxide are apparently supported, the broad recitation of a metal-ion catalyzed oxidative condition appears to be beyond the scope of enablement provided by the specification and prior art.

Claims16-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method wherein the first sample and the second sample are derived from the same source, does not reasonably provide **enablement** for the first and

second sample not derived from the same source. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The limitation of claim 27 wherein the first and second sample are derived from the same source is essential to the comparison of the samples in the method as recited in claims 16-26 and 28.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the invention in full scope with the claims without further undue experimentation.

Claim Rejections - 35 USC § 112, Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention. Claims 17-20 recite the limitation "the aggregation inhibitor" in line 1 of claims 17 and 19. There is insufficient antecedent basis for this limitation in the claim. Claims 17-20 depend from claim 16, a method for identifying "an inhibitor of NACP/α-synuclein aggregation"

and should be correlated to claim 16. The lack of antecedent basis for "the aggregation inhibitor" makes the scope of the claim indeterminate.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Instant application claims priority from 60/103,310 filed 10-6-1998. Applicants should note the new matter rejection of record with respect to the priority document of 10-6-1999. Support for the claim recitations is similarly not found within the prior '310 provisional application. Accordingly, the effective filing date awarded instant claims is the date of 11-13-01 absent evidence for support in both instant applications (371 of PCT/US99/23134, 10-6-1999 and the provisional 60/103,310, 10-6-1998 as filed).

Applicant's traversal (in remarks, 8-5-04) of the priority determination as set forth in the new matter rejection is noted. Applicant argues that one of ordinary skill in the art would have

readily recognized from the disclosure of the provisional application taken with the knowledge in the relevant art that metal-ion catalyzed oxidative conditions could be used to facilitate NACP/α-synuclein aggregation. As noted above by the Examiner, as set forth above, evidence of support is not established for the contemplation of "metal-ion catalyzed oxidative conditions" or for "ferrous ion other than ferrous ion with hydrogen peroxide" as newly recited. Thus, the priority date of claims 16-28 is the date of 11-13-01 absent further support in the specification and priority document as filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 16-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Hashimoto *et. al.*, *NeuroReport* 10:717-721, 1999. Claims 17-20 are rejected as they depend from claim 16.

Hashimoto *et. al.*, teach that the iron chelator, deferoxamine able to inhibit the iron-catalyzed oxidative reaction that stimulated aggregation, see in particular abstract, Results, pp 718-20 and Figures 1-2. Hashimoto *et. al.*, teach a method including "inducing aggregation of α-synuclein by iron-catalyzed oxidative condition in samples that comprises α-synuclein, exposing the samples to a test compound, measuring aggregation of NACP/α-synuclein and comparing the aggregation level of α-synuclein, wherein less aggregation indicates the test compound is an inhibitor of aggregation. The reference teaches the method wherein the sample comprises cells that express α-synuclein, iron ions from ferric and ferrous chloride, samples from the same source, and human recombinant NACP/α-synuclein. Thus, Hashimoto meets the claim limitations in that it teaches that an iron-catalyzed oxidative reaction induced via ferric ion and/or ferrous ion and hydrogen peroxide is effective to increase aggregation of α-synuclein and that deferoxamine inhibits α-synuclein aggregate formation.

Claims 16-20 arerejected under 35 U.S.C. 102(b) as being anticipated by Jensen *et. al.*, *Biochem. J.*, 323:539-546, Apr. 15, 1997 as evidenced by Harris *et. al.*, *Experimental Neurology*, 1995, 131(2):193-202.

Jensen *et. al.*, teach that, "the identification of peptides that bind Abeta might open new possibilities for preventing the formation of AD plaques," the major pathology associated with Alzheimer's disease, see in particular pp. 545, column 2, lines 5-14. Jensen's "strategy is to identify small peptides that inhibit Abeta self-aggregation and the formation of complexes between Abeta and synucleins and their fragments . . . , and suggests studies should show

whether peptides derived from synucleins might prevent aggregations and whether they might be used as substances for the construction of drugs." Thus, Jensen *et. al.*, teach a method for the identification of molecules that inhibit aggregation of Abeta and synucleins. Jensen *et. al.*, teach a method for inducing aggregation of amyloidogenic proteins, see in particular Experimental, pp. 540, column 2, lines 24-44, and Results, Aβ binding to α- and β-synuclein, pp. 541-542, Figures 1-3. The amyloidogenic proteins were subject to treatment with BS3 cross-linker and the specificity of binding to alpha-synuclein was measured via SDS-PAGE analysis. Other treatments include incubation or exposure to Abeta, NAC, SDS, or β-synuclein. Jensen is silent as to Abeta being subjected to a metal-ion oxidative condition. However, Harris *et. al.*, teach direct evidence of oxidative injury produced by beta-amyloid peptide. Thus, as evidenced by Harris, the contact of Abeta as taught by Jensen is equivalent to exposure to an oxidative condition, which as noted by Jensen provides for aggregation of NACP/alpha-synuclein. Jensen also teaches such measurements in the presence or absence of β-synuclein, Aβ and NAC. It was also shown that α-synuclein can form homodimers or heterodimers with β-synuclein, electively teaching that β-synuclein can compete with α-synuclein for binding, see in particular Figure 4, and pp. 542, columns 1-2 paragraph spanning. Thus, Jensen teaches, "'exposing amyoidogenic proteins to a treatment, measuring aggregation of α-synuclein to test for a decrease in aggregation wherein a decrease is indicative of inhibition." Further, Jensen notes that the complex formation is SDS sensitive. Thus, Jensen teaches that SDS, Aβ peptide, NAC and β-synuclein each compete or serve to inhibit α-synuclein aggregation and binding. Each of these results exhibit competition for α-synuclein aggregation/binding and thus are tests for decreases in aggregation as the molecules inhibit the formation of complexes. As claimed in claim 19-20,

the method of Jensen includes exposure to the agent beta-synuclein and thus the reference encompasses the beta-synuclein agent that promotes the expression of anti-amyloidogenic proteins. Thus, Jensen *et. al.*, teach "A method for identifying an inhibitor " the steps of "inducing protein aggregation in a first sample comprising NACP/alpha-synuclein by exposing a first sample to an metal-ion catalyzed oxidative condition, exposing the first sample to a treatment, inducing protein aggregation in a second sample comprising NACP/alpha-synuclein by exposing a second sample to the oxidizing agent, measuring an aggregation level of NACP/alpha-synuclein in the first sample and the second sample and comparing the aggregation level of NACP/alpha-synuclein in the first sample with the aggregation level of NACP/α-synuclein in the second sample wherein less aggregation in the first sample is indicative of an inhibitor of aggregation." Thus, the reference teachings anticipate the claimed invention.

Claims 16, 21-22, 24-28 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Wolozin *et. al.*, US Patent 6,780,971, filed 7-9-2001 and issued 8-24-04. Claims 17-20 and 23 are rejected as they depend from claim 16.

Wolozin *et. al.* teach a method of identifying factors that inhibit aggregation of α-synuclein in vitro or in living neurons. The method comprises adding the agent to a neuronal cell sample containing α-synuclein, including human recombinant α-synuclein, in the presence of exogenous iron from $FeCl_2$, and allowing the α-synuclein to aggregate, determining the amount of aggregation of α-synuclein, and then comparing that amount with an amount determined in a control sample in which the agent is absent. A decrease in the amount of aggregation indicates that the agent is capable of inhibiting the aggregation of α-synuclein. The reference teaches samples derived from the same source that comprises neuronal cells that express human

recombinant α-synuclein. Thus, Wolozin meets the claim limitations in that it teaches a method of identifying an inhibitor of aggregation induced by an iron-catalyzed oxidative reaction.

Claims 16, 21, 24-27 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by Biere *et. al.*, US Patent 6,184,351 filed 9-24-1999 and issued 2-6-2001 or in the alternative, under 35 U.S.C. 103 as obvious over Biere *et. al.*, US Patent 6,184,351 filed 9-24-1999 and issued 2-6-2001.

Claims 17-20, 22-23, and 28 are rejected as they depend from claim 16.

Biere *et. al.*, also provide an in vitro aggregation assay, which can be utilized to identify α-synuclein nucleation inhibitors. Thus, Biere teaches "A method for identifying an inhibitor of NACP/α-synuclein aggregation" as claimed. The method of Biere *et. al.*, teaches exposure to a potential nucleation-affecting agent, see in particular claim 4 and thus, Biere et al., teach a method comprising providing a test compound. The assay includes generating a solution of α-synuclein, see in particular claim 4 and thus Biere *et. al.* teach providing samples wherein the samples comprise cells that express NACP/α-synuclein. As set forth in Biere *et. al.*, the samples are compared to assess inhibition as indicated by levels of aggregation in samples. Thus, Biere *et. al.*, teach the steps of "inducing protein aggregation in a first sample comprising NACP/α-synuclein, exposing the first sample to a treatment, inducing protein aggregation in a second sample comprising NACP/α-synuclein, measuring an aggregation level of NACP/α-synuclein in the first sample and the second sample and comparing the aggregation level of NACP/α-synuclein in the first sample with the aggregation level of NACP/α-synuclein in the second sample wherein less aggregation in the first sample is indicative of an effective treatment." Thus, the Biere reference teaches all of the limitations of claim 16 but does not teach inducing

aggregation by subjecting the samples to a metal-ion catalyzed oxidative condition. The Examiner is unable to determine whether or not exposure of the α-synuclein or aggregation competent fragments of α-synuclein or the mutants to the cell (claim 4) provides for the specific property of exposing the samples to a metal-ion catalyzed oxidative condition. Exposure to the solution comprising α-synuclein induces aggregation of NACP/α-synuclein and thus seem to be identical in characteristics or properties to that claimed of exposing to a metal-ion catalyzed oxidative condition, the USPTO has insufficient resources and facts to determine whether the respective exposure is "inherently the same" or "obvious" because the Examiner cannot determine whether the exposure of the solution that comprises α-synuclein induces aggregation by a metal-ion catalyzed oxidative condition. The Examiner is not in a position to determine inherency or obviousness because the record does not establish how the steps are the same or differ. Since the record does not allow such determination, the burden shifts to Applicants to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re* Best 195 USPQ 430, 433 (CCPA 1977).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hashimoto *et. al.*, *J Biol Chem* 274(41):28849-28852 in view of Wolozin *et. al.*, US Patent 6,780,971, filed 7-9-2001 and issued 8-24-04 and further in view of Narhi *et. al.*, J Biol Chem, 274(14):9843-9846, 1999. The reference teaches a method of identifying an inhibitor of aggregation induced by an iron-catalyzed oxidative reaction. The reference further teaches the iron-catalyzed oxidative reaction is attributed to the cytochrome c/H_2O_2-induced aggregation of α-synuclein and that cytochrome c is co-localized with α-synuclein in the substantia nigra in brain samples from Parkinson's disease patients.

Hashimoto does not teach the method of identifying inhibitors in the substantia nigra brain samples wherein the neuronal cells express α-synuclein. However, it would have been obvious to one of ordinary skill in the pertinent art in view of the teachings of Wolozin *et. al.*, which teaches the method of inhibiting, can be performed in vitro, in a cell culture system or animal model (See column 4, line 66-67), in particular using neuroblastoma cells (See column 5, line 38) and Narhi that suggests methods of identifying inhibitors can be adapted to high throughput screening for compounds that block α-synuclein aggregation (p. 9846, column 2) that the method of identifying inhibitors may be performed with the samples using neuronal cells that express α-synuclein, including brain samples from the substantia nigra. The art recognizes that α-synuclein is expressed in neuronal cells (See pg 1319 "Expression of a-synuclein" in Perez and Hastings, Journal of Neurochemistry, 89(6):1318, 2004). Furthermore, one would have been motivated by the recognition in the art that point mutations in α-synuclein are associated with Parkinson's disease and diseases with Lewy bodies and that compounds that inhibit α-synuclein aggregation may be useful therapeutics (See Nahri p.9846, column 2).

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under

37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Johnalyn Lyles whose telephone number is 571-272-3433. The examiner can normally be reached on M-F 8 am - 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

jdl